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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/652,345	08/31/2000	David H. Farb	0146-2026	2909

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EXAMINER
LI, RUIXIANG

ART UNIT	PAPER NUMBER
1646	14

DATE MAILED: 12/03/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/652,345	Applicant(s) FARB ET AL.	
	Examiner Ruixiang Li	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *12-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,and 26-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08/31/2000* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicants' election of Group I, claims 1-33 in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse.
2. During a telephone conversation with Kevin M. Farrell on October 1, 2001, species A (NMDA receptors with identical NR2 subunits and different NR1 subunits) within Group I was elected. Thus, claims 12-25 are withdrawn from considerations because of applicants' election of species. Affirmation of this election must be made by applicant in replying to this Office action.
3. Claims 1-57 are pending, Claims 12-25 are withdrawn from consideration, and Claims 1-11 and 26-33 are under consideration.

Objections to the Specification/Drawings

4. The disclosure is objected because of the following informalities: (i) Abbreviations used in the specification, such as PS and AMPA, are not given (the examiner assumes that PS stands for pregnenolone sulfate and AMPA means α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate); and (ii) Reference numbers in specification do not correspond to same elements in drawings. For example, Figures

1(A)-1(F) on page 4 actually are Figures 2 (A)-2 (F) and Figures 2(A)-2(E) on page 5 are Figures 3 (A)-3(E). Appropriate correction is required.

5. The drawings are objected to because (i) Figs. 2-4, 6-8, 10, 12-17, 19, 20, 22, 26-29 are not labeled separately or properly; (ii) Lines, numbers and letters in Figs. 10, 31, and 32 are not uniformly thick and well defined; (iii) numbers and reference characters in Figs. 5 and 12 are not plain and legible; and (iv) Fig. 1 appears to be a prior art drawing (Durand, et al. *Proc. Natl. Acad. Sci. USA* , 90: 6731-6735, 1993) and it should be labeled as such. Correction is required (please see attached form PTO 948 for details).

Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Claim Rejections—35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the subset of the NMDA receptors" in the 2nd line of claim 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections—35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2, and 26-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Park-Chung et al. (IDS, Paper # 7, *Mol. Pharmacol.* 52 :1113-1123, 1997). Park-Chung et al. teach a method of identifying subunit specific steroid modulators of the N-methyl-D-aspartate (NMDA) receptor in *Xenopus laevis* oocytes expressing $NR1_{100}$ and NR2A subunits (see, in particular, page 1119, 2nd paragraph of left hand column). Chung et al. also teach that the response of NMDA receptor to agonists (NMDA, glutamate, and glycine) or antagonist (APV, D-2-amino-5-phosphonovaleric acid; Fig. 7 and page 1119, 3rd paragraph of left hand column) were modulated by steroid modulators (e.g., pregnenolone sulfate and 3β5βS (3β-hydroxy-5β-pregnan-20-0ne sulfate), or by non-steroid modulators (e.g., spermine and redox; page 1113, summary). Thus, the reference by Chung et al. meets the limitations of claims 1, 2, and 26-33.

10. Claims 1, 2, 26-29, and 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Durand et al. (*Proc. Natl. Acad. Sci. USA* 89:9359-9363, 1992). Durand et al. teach differential potentiation by spermine of NMDA receptors with

NR1a and NR1b subunits that are expressed in oocytes (page 9361, 2nd paragraph of right hand column–page 9362, 1st paragraph and Fig. 4). Durand et al. also teach NMDA receptor agonists (e.g., NMDA, glutamate, and glycine) and antagonists (see Table 1). Durand et al. further disclose modulatory effects of kinase modulators on responses of NMDA receptors with NR1a and NR1b subunits (Fig. 5 and Table 2). Thus, the reference by Durand et al. meets the limitations of claims 1, 2, 26-29, and 31-33.

11. Claims 1-6, 26-28, 31, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al. (*Mol. Pharmacol.* 45:803-809, 1994). Williams et al. teach the characterization of differential modulatory effects of spermine on NMDA receptors with identical NR2 subunits and different NR1 subunits expressed in oocytes, including NR1A/NR2A and NR1B/NR2A (Fig. 1). Please note that NR1A is $NR1_{011}$ whereas NR1B is $NR1_{111}$. NR1B contains an α exon. Williams et al. also teach NMDA receptor agonists (NMDA, glutamate, and glycine; Figs. 4 and 6). Thus, the reference by Williams et al. meets the limitations of claims 1-6, 26-28, 31, and 33.

12. Claims 1-5, 7, 26-29, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Daggett et al (U.S. Patent number 5,849,895, 12/15/1998). Daggett et al. teach NMDA receptor subunits, homomeric and heterometric NMDA receptors comprising these subunits (column 15, 2nd paragraph), and methods for using such receptor subunits (column 2, 4th paragraph) to identify and characterize compounds which affect the function of such receptors, e.g., agonists, antagonists, and modulators (see, in particular, column 16, 3rd paragraph—column 17, 4th paragraph;

Table 1). Daggett et al also teach NMDA receptors with identical NR2 subunits and different NR1 subunits expressed in oocytes (Table 1), chimeric isoforms of NMDAR1A, for example, NMDAR1-I63-delta-363 (See example 2, section D), as well as NMDA receptor agonists (NMDA, glutamate, and glycine; Table 1). Please note that NMDAR1A is $NR1_{011}$. Daggett et al further teach modulation of the ion channel activity of NMDA receptors by subunit-specific antibodies (column 18, 4th paragraph). Thus, the reference by Daggett et al meets the limitations of claims 1-5, 7, 26-29, and 31.

13. Claims 1-5, 8, 26-29, 31, and 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Masuko et al. (Mol. Pharmacol. 55:957-969, June 1999). Masuko et al. teach various mutations in the NR1 subunit (NR1A or NR_{011}) of NR1/NR2B receptors expressed in *Xenopus oocytes and* changes in sensitivity of these variants to spermine (a non-steroid modulator), NMDA receptor agonists (glutamate and glycine) and antagonist (ifenprodil) (see Figs. 1-8). Thus, the reference by Masuko et al. meets the limitations of claims 1-5, 8, 26-29, 31, and 33.

14. Claims 1-6, 8, 11, 26-28, 31, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Traynelis et al. (J. Neurosci. 18:6163-6175, 1998). Traynelis et al. teach differential responses of point mutants of NR1 subunits (NR1a and NR1b) of various NR1/NR2 receptors expressed in *Xenopus oocytes* to glutamate and glycine modulated by spermine and zinc (see, in particular, Fig. 3). Please note that point mutants of NR1b contain an α exon. Thus, the reference by Traynelis et al. meets the limitations of claims 1-6, 8, 11, 26-28, 31, and 33.

Claim Rejections—35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Daggett et al. (U.S. Patent number 5,849,895, 12/15/1998) in view of Masuko et al. (Mol. Pharmacol. 55:957-969, June 1999).

Daggett et al teach methods for using receptor subunits to identify agonists, antagonists, and modulators of NMDA receptors recited in the claims, as discussed above. Daggett et al do not teach the use of NR1 subunit containing point mutations specifically at a residue at 182, 193, 202, 233, or 252.

Masuko et al. teach methods for using NR1A subunit with various point mutations to identify the sites of actions of spermine and ifenprodil on NMDA receptors, as discussed above. Theses various point mutations at NR1A subunit include point mutations at a residue at 181, 192, 198, 227, 251 or 253 (See Fig. 2).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the methods of Daggett et al so as to include the point mutants of NR1a subunit recited in Claim 9 with a reasonable expectation of success. The motivation to do so would have been in the recognition that determination of the effect of the drug substances on specific receptor mutations

should permit development and screening receptor subtype-specific or disease-specific drugs and reduction of unwanted side effects, as suggested by Daggett et al. (U.S. Patent number 5,849,895, 12/15/1998, column 15, 4th and 5th paragraphs).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**yvonne.eyler@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ruixiang Li
Examiner
November 28, 2001

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